Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Antimicrobial Agents 57 (2021) 106306

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Letter to the Editor

Effect of hydroxychloroquine and azithromycin on the viral clearance of SARS-CoV-2: response to Hervé Seligmann

Dear Editor,

We read Hervé Seligmann's balanced comments regarding our work with great interest [1]. He raises the possibility of false negative PCR results that may have possibly influenced our results. However, it is worthy to note that the negative results at end of our follow-up were preceded by two or more negative tests in 93% of the treated patients, and that we used an internal control of PCR. Regarding missing PCR data, the results were considered positive if the PCR results performed the day before and the day after were both positive. In contrast, they were considered negative if the results of at least one of the two previous consecutive days were negative (according to the European Centre for Disease Prevention and Control, the patients can be discharged from hospital if at least two consecutive RT-PCR tests are negative in respiratory samples (https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-guidance-discharge-and-ending-isolation-firstupdate.pdf)).

Hervé Seligmann's statistical approach in analysing our data on the effect of hydroxychloroquine and azithromycin on the viral clearance in COVID-19 patients [2] is pertinent and shows evidence of a cumulative, systematic and gradual effect of the treatment on reducing SARS-CoV-2 carriage. Following suggestions from other colleagues we reanalysed our data without patient exclusion and using some statistical methods better adapted to small series, including Barnard and Wang tests; estimates of effect modification such as relative risk reduction, absolute risk reduction and number needed to treat; mixed effect logistic regression model; and logistic and linear regression models [3–6]. These different approaches confirmed our results. Toumi and Aballea reanalyzed our results using the last-observation-carried-forward imputation conservative method and also confirmed our results [7]. Finally, a meta-analysis of available studies evaluating the effect of hydroxychloroquine on SARS-CoV-2 clearance confirmed the significant effect of this drug [8].

In conclusion, despite the many passionate and sometimes acerbic criticisms that our imperfect study has raised, it clearly seems that our results are robust and confirm the need for large-scale studies on the effect of hydroxychloroquine and azithromycin on both SARS-CoV-2 clearance and clinical benefit in COVID-19 patients.

References

[1] Seligmann H. Balanced evaluation of preliminary data on a candidate COVID-19 hydroxychloroquine treatment. *Int J Antimicrobial Agents* (in press).
[2] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;56(1):105949.
[3] Gautret P, Hoang VT, Lagier JC, Raoult D. Response to advances statistical methods and designs for clinical trials for COVID-19. Int J Antimicrob Agents 2021;57(1):106235.
[4] Gautret P, Hoang VT, Lagier JC, Raoult D. Response to effect estimation of hydroxychloroquine for COVID-19: a secondary analysis of an open label non-randomized clinical trial. Int J Antimicrob Agents 2021;57(1):106237.
[5] Gautret P, Hoang VT, Chaudet H, Lagier JC, Raoult D. Response to uncertain effect of hydroxychloroquine and azithromycin on SARS-CoV-2 viral load. Int J Antimicrob Agents 2021;57(1):106244.
[6] Gautret P, Hoang VT, Lagier JC, Raoult D. Effect of hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, an update with an intention-to-treat analysis and clinical outcomes. Int J Antimicrob Agents 2021;57(1):106239.
[7] Toumi M, Aballea S. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial. by Gautret et al.. J Mark Access Health Policy 2020;8(1):1758390.
[8] Million M, Roussel Y, Gautret P, Raoult D. Effect of hydroxychloroquine and azithromycin on SARS-CoV-2 clearance in COVID-19 patients, a meta-analysis. Int J Antimicrob Agents 2021;57(1):106240.

Philippe Gautret
IHU-Méditerranée Infection, Marseille, France
Aix Marseille Univ, IRD, AP-HM, SSA, VITROME, Marseille, France

Van Thuan Hoang
IHU-Méditerranée Infection, Marseille, France
Aix Marseille Univ, IRD, AP-HM, SSA, VITROME, Marseille, France
Thai Binh University of Medicine and Pharmacy, Thai Binh, Vietnam

Philippe Colson, Didier Raoult*
IHU-Méditerranée Infection, Marseille, France
Aix Marseille Univ, IRD, APHM, MEPHI, Marseille, France

*Corresponding author.

DOIs of original articles: 10.1016/j.ijantimicag.2020.105949, 10.1016/j.ijantimicag.2021.106292

https://doi.org/10.1016/j.ijantimicag.2021.106306